REMARKS

Pending claims 206-209, 209, 211-214, 216, 217 and 225-228 are variously rejected under 35 U.S.C. § 103 and § 112, first paragraph. The claims are also provisionally rejected under the judicially created doctrine of obviousness-type double patenting.

I. PRELIMINARY REMARKS

The Applicants thank Examiner Gembah and her supervisor Examiner Marschel for the courtesy of a telephonic interview on April 22, 2008. In the interview, the cited art was discussed. In the Interview Summary, the Examiner stated that Applicants used a different model than that provided in Rossoni *et al.* However, the Applicants pointed out that the model described in Rossoni *et al.* is irrelevant to the invention because it does not mimic the events leading up to the formation of plaques and the physiological effects leading up to plaque formation and eventually a myocardial infarction (MI). The Applicants did not claim to use an animal model in the interview.

Claim 228 is amended by the foregoing amendment. This amendment is supported at page 6, lines 20-26 of the specification. Therefore, this amendment does not add new matter to the application.

II. INFORMATION DISCLOSURE STATEMENT

In the Office Action, the Examiner acknowledged receipt of the Information Disclosure Statement submitted on November 30, 2007. However, the Examiner continues to refuse to consider documents C121-C129, stating that these documents are not considered published documents. The documents listed in the International Search Reports of C121-C129 were individually submitted to the Patent Office with the Information Disclosure Statements dated April 13, 2005, July 13, 2005, January 13, 2006, January 30, 2007 and May 3, 2007.

However, the Applicants reiterate that the PTO may wish to consider documents C121-C128 because they are foreign search reports, not because they are published references. While the Patent Office may choose not to list the documents as "references" on the face of an eventual patent, there is no rule stating that only "publications" may be submitted by an applicant or considered by an examiner.

Document C129 is a Genbank entry that should be considered as a publication, and the Applicants continue to urge the Examiner to consider this document. A copy of this reference was submitted with the previous information disclosure statement; therefore this document is not enclosed.

III. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

The Patent Office maintained the rejection of claims 212 and 213 under 35 U.S.C. § 112, first paragraph for alleged lack of written description of the term "pro-drugs" as used in the claims. In order to expedite prosecution, the term "pro-drug" is omitted from amended claim 212. However, Applicants continue to maintain their position that pro-drugs are adequately described by the specification for the reasons set out in the previous response. The essential structure of the prodrug is conveyed, *e.g.*, by the description of the structure of the drug itself.

In view of the foregoing amendment, the rejection of claims 112 and 113 under 35 U.S.C. § 112, first paragraph is now moot. Applicants request that this rejection be withdrawn.

IV. THE REJECTION UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

The Patent Office rejected claims 206-209, 211-214, 216-217 and 226 under 35 U.S.C. §103, alleging that the claimed invention was obvious in view of a combination of *at least eight* references in combination. The Applicants respectfully traverse.

A. The claimed invention

The Examiner must consider the claimed invention when making a determination of obviousness. According to MPEP 2142, the Examiner must make a determination whether the ***claimed invention*** "as a whole" would have been obvious to a person of ordinary skill in the art at the time just before the invention was made.

One of the deficiencies of the current rejection is that the Patent Office has alleged that "the invention" is obvious without focusing on the claim limitations, and how they relate to each other to define the invention. Should the Patent Office maintain any

rejections under §103, the Applicants request that the rejection explain how methods that include *at least* each of the limitations summarized below would have been obvious.

1. Claims 206-209, 211-214, 216-217, and 226.

The first rejection under §103 pertains to claims 206-209, 211-214, 216-217, and 226.

Claim 206 is directed to *a method of reducing C-reactive protein (CRP)* in a *human subject*. The claim specifies a first step of selecting a human subject *at risk for* MI; and a step of administering a leukotriene synthesis inhibitor, such as BAY-X-1005 (dependent claim 212), in an amount effective to reduce serum CRP in the subject. The Examiner has entirely failed to identify a reference that suggests that such a leukotriene synthesis inhibitor could be used effectively to reduce CRP in any human population, let alone a population at risk for MI.

Some of the claims include a limitation specifying particular parameters for selecting a subject for treatment. For example, claim 206 specifies selecting a human subject *at risk for* myocardial infarction (MI). Claim 209 specifies selecting a human subject susceptible to primary myorcardial infraction, e.g., a subject that has not already suffered a myocardial infraction. Although the Examiner cites a reference involving an animal model that mimicks MI (Rossoni) and a reference that studies patients post-MI, the Examiner fails to address the claim relating to a subject that has not already suffered MI.

Some of the claims specify steps for monitoring efficacy of the treatment. For example, claim 214 specifies monitoring an inflammatory marker. Claim 207 specifies measuring CRP to monitor efficacy. Claim 215 specifies monitoring a different marker, MPO. Claim 216 specifies monitoring a leukotriene level. Claim 216 depends from claim 215 and further specifies monitoring CRP (in addition to the leukotriene level). The Examiner has failed, for example, to cite any literature suggesting to monitor CRP or MPO in a regimen involving a FLAP inhibitor.

2. The rejection of claims 225, 227, and 228.

The second rejection under §103 pertained to claims 225, 227, and 228. Claim 225 introduces the limitation of determining a FLAP genotype or haplotype of a human subject, and selecting for treatment a human subject with a FLAP genotype or haplotype that correlates with an increased risk of myocardial infarction. Much of the specification describes detailed human population studies that identified polymorphisms in the FLAP gene that correlate with increased risk of MI. The Examiner has failed to cite any reference that discloses or suggests that a human population can be stratified with respect to risk for MI based on polymorphisms/haplotypes in the FLAP gene.

B. Analysis of the teachings of the prior art (without hindsight consideration of the invention), and the rejection based on seven references.

The Examiner's rejections rely on seven or eight prior art references in combination. The fact that the Examiner finds it necessary to select so many references to attempt to establish obviousness is, itself, evidence that the invention was unobvious. Below is an analysis of some of the teaches of the cited references; an explanation that it would have been unobvious to combine these references; and an explanation that any combination of the references would still fail to suggest the invention or provide a reasonable expectation that it would be successful.

1. Hatzelmann *et al.*, *Agents Actions* 43: 64-68, 1994

Hatzelmann *et al.* is a review article that describes the *mode of action* of BAY-X-1005 as a leukotriene synthesis inhibitor, and discusses the use of BAY-X-1005 to elucidate the biological interaction of FLAP and 5-Lipoxygenase (5-LOX). The article does not describe studies with patients, or treatment regimens at all. This article mentions that inhibition of 5-LOX is contemplated as a potential therapy for allergic asthma and other inflammatory disease, but it is merely a mention at the beginning and end, to provide some context. This article is silent on the effect of BAY-X-1005 on pro-inflammatory markers outside of the leukotriene synthesis pathway. Notably, the article is silent with respect to CRP. As indicated in the attached schematic of the leukotriene synthesis pathway, CRP is not known to play a role in leukotriene synthesis pathway. (See Exhibit A).

The Examiner states that even though this article is silent in regards to MI, Hatzelmann *et al.* renders administration of an effective amount of leukotriene synthesis inhibitor, as recited in claim 214, obvious. Clearly, this is putting the cart before the horse. It is impossible for Hatzelmann *et al.* to render obvious *an amount effective to reduce serum CRP* when Hatzelmann *et al.* makes no mention of CRP or the ability of a leukotriene synthesis inhibitor to reduce CRP.

The Examiner asserted that because Hatzelmann *et al.* teaches BAY-X-1005 inhibits FLAP, administration of an effective amount of the drug to reduce CRP in a human subject allegedly would be obvious. However, Hatzelmann *et al.* does not describe oral administration of BAY-X-1005 in detail, and only describes studies in cells, *e.g.* human PMNLs and HL-60 cells, to study the biological *mechanism* of action of BAY-X-1005. This article does not provide any indication of an effective dose to reduce any inflammatory marker, let alone to reduce CRP, a marker unrelated to the leukotriene synthesis pathway. There is no basis to conclude that Hatzelmann *et al.* would have motivated a skilled artisan to administer a leukotriene synthesis inhibitor to reduce CRP levels, or provide any guidance as to an effective dose for this purpose.

2. Mazzone *et al., J. Am. College of Cardiol.* 38: 1895-1901, 2001

The Examiner alleged that Mazzone *et al.* "teach as evidence" that MI correlates to inflammation.

In actuality, Mazzone *et al.* investigated the levels of a selection of pro-inflammatory cytokines (IL-1, IL-6, TNF-α, and IFN-γ) in patients with silent myocardial ischemia. Ischemia is not infarction. "Cytokine levels were detected only once in the study, and our observational study did not include any follow-up controls." (Mazzone *et al.* at p. 1899, "study limitations" paragraph.) This study does not measure the levels of CRP or leukotrienes in these patients, and does not consider whether elevated levels of CRP might be associated with risk for MI. This article does not provide a skilled artisan any insight into administering a leukotriene synthesis inhibitor to patients at risk of MI in order to reduce CRP levels.

A large number of cytokines and proteins are known to be associated with inflammation. It unreasonable to conclude that since a disease is associated with

inflammation, one of skill in the art will know which pro-inflammatory proteins are associated with a particular disease without a specific teaching. The field is too vast to make general conclusions regarding markers for inflammation and particular disease states. In fact, Mazzone *et al.* further teaches that in "patients with asymptomatic ischemia, there is a higher production of anti-inflammatory cytokines ...." (P. 1897.) The mere allegation that MI is associated with inflammation does not provide any indication that leukotriene synthesis inhibitors would be effective in reducing the level of a single inflammatory marker, CRP, that is not known to play a role in the leukotriene synthesis pathway.

3. Pietila *et al.*, *Eur. Heart Journal* 17: 1345-1349, 1996

Pietila *et al.* reported that patients having a high peak serum CRP level in the first day *after an suffering an acute MI* also have an increased risk of mortality within six months while being treated with thrombolytic drugs. Thus, the authors concluded that CRP levels may play a role in *selecting MI patients* for therapies such as ACE inhibitors and amiodarone. This study merely investigated mortality rate and CRP levels in patients receiving *thrombolytic therapy* after suffering an MI. The study concludes, "reduction of inflammatory reaction *by successful thrombolytic treatment* may make an important contribution to the survival benefit." (See abstract, emphasis added.) This study does not disclose or suggest administering a leukotriene synthesis inhibitor, and provides no information regarding administration of leukotriene synthesis inhibitors and the effect of these drugs on CRP level in MI patients. (If anything, the focus on use of *thrombolytic treatment* would dissuade a researcher interested in leukotriene inhibitors from considering this study.)

There is no reason a skilled artisan would have been motivated to apply data relating to the CRP levels in *post-MI* patients receiving thrombolytic therapy to draw any conclusion about leukotriene synthesis inhibitor therapy. Thrombolytic drugs are administered to dissolve blood clots rather than directly inhibit inflammation. Therefore, thrombolytic drugs and leukotriene synthesis inhibitors have different modes of biological action, and data relating to one therapy would not have been considered pertinent to methods using the other therapy. The mere fact that CRP levels were observed to be elevated *after* MI does not motivate one of skill in the art to administer a leukotriene synthesis inhibitor to

reduce CRP levels. Likewise, the fact that CRP levels were observed to be elevated *after* MI does not provide information about CRP levels of individuals *at risk* for MI. The fact that CRP rises after MI provides no insight into CRP levels before MI, or about effective ways to reduce CRP before MI.

4. The Invention is Not Obvious in View of the Combination of Hatzelmann, Mazzone and Pietila

The Examiner asserted that one of skill in the art would have combined Hatzelmann *et al.* Mazzone *et al.*, and Pietila *et al.* to arrive at the claimed invention "because BAY-X-1005 has been used to treat inflammatory disease. It is taught the myocardial ischemic is an inflammatory disease." (See p. 6 of the Office Action).

This analysis is faulty. First, the Examiner seems to be equating ischemia and infarction. Mazzone *et al.* makes clear that silent versus symptomatic ischemia have different cytokine profiles, and neither population is equivalent to the post infarction population studies by Pietila. Second, of the three references cited, Hatzelmann *et al.* is the only one that mentions BAY-X-1005, and that reference does *NOT* teach that BAY-X-1005 has been used to treat inflammatory disease. Hatzelmann *et al.* is an investigation of the biochemical/pathway role of FLAP, which the authors conclude is complicated. (See p. 67, conclusion.) The authors express "hope" that 5-LOX inhibitors, represented by BAY-X-1005, as future drugs will provide substantial benefit to patients suffering from inflammatory and/or allergic disease.

Third, inflammation is too tenuous a connection to attempt to select and link the three selected references, one of which (Hatzelmann) deals with the biochemical pathway role of FLAP and regulation of 5-LOX (and makes no mention of MI); the second of which (Mazzone) deals with production of inflammatory *cytokines* in patients with silent myocardial ischemia, and has nothing whatsoever to do with FLAP or 5-LOX; and the third of which (Pietila) pertains to serum CRP in acute myocardial *infraction* patients and throbolytic treatment for MI, and has nothing to do with FLAP, 5-LOX, silent ischemia, or cytokines. If "inflammation" is the only common link, then the Examiner should explain why these three documents would have been chosen and combined by a person of ordinary skill. A person of ordinary skill who searched "inflammation or inflammatory" in the PUBMED database

would currently identify more than 500,000 non-patent publications. The only possible basis for choosing these three publications was hindsight.

Only one of these three references, Pietila *et al.*, mentions CRP, and this reference notes that CRP is an acute phase reactant that rises due to various stimuli, including myocardial infarction. Neither Pietila *et al.* nor the other references draw a connection between leukotrienes and CRP, or suggest using a leukotriene inhibitor to reduce CRP. Likewise, these references (alone or in combination) are silent in regards to any reasonable expectation of success that administration of a leukotriene synthesis inhibitor would have for reducing the levels of CRP in a human subject **at risk for** MI.

The Examiner states that myocardial ischemic is the cause of high concentrations of CRP, but presumably is referring to Pietila's teachings that acute myocardial *infarction* causes elevated CRP. Assuming that this is the case, it is important to consider what the prior art as a whole taught about the use of anti-inflammatories and MI. Recently, there have been prominent reports raising questions about the benefit or harm of certain other anti-inflammatory agents, (*e.g.*, VIOXX®, high-dose CELEBREX®, naproxen) on cardiovascular system of recipients and some anti-inflammatory agents are thought to *increase the risk* of heart attacks in patients (American Heart Association (2005, November 14) Science Daily. Retrieved November 29, 2007, http://www.sciencedaily.com/releases/2005/11/051114112914.htm; Exhibit B) Clearly, both the motivation to select the particular treatment claimed, and expectation of success, would have been lacking from the prior art as a whole.

5. Rossoni *et al.*

The Examiner continues to assert that cite Rossoni *et al.* teaches one of ordinary skill in the art to monitor leukotrienes after administration of BAY-X-1005. The Examiner also stated that Rossoni *et al.* teaches BAY-X-1005 exerts significant cardioprotection. For the reasons set out in the response to the previous office action, Rossoni *et al.* is irrelevant to the claimed invention.

Rossoni *et al.* teaches that pretreatment with BAY-X-1005 protected the rabbit ischemic heart from increased coronary perfusion pressure and injury related to an acute MI *induced by coronary artery ligation*. Rossoni *et al.* describes an animal model

that purports to model an infarction (coronary artery ligation) and then studies what effects a drug has post-infarction. It is not clear what Rossoni *et al.* contributes to the knowledge about the benefit of the drug regime tested in the post-infarction model that was employed.

The Examiner's stated reason for combining Hatzelmann, Mazzone, and Pietila *et al.* related to inflammation, calling into question any motivation for combining Rossoni *et al.*. The rabbit model used by Rossoni *et al.* does not at all mimic the biological events *leading up to* the formation of plaques, the development of inflammation, an increase in CRP levels or the ultimate rupture of the plaque. The model purports to mimic the ultimate post-injury result, *i.e.* what happens after blockage of the coronary artery, but such a model is not useful for assessing the capability of a potential therapy to either reduce CRP levels, to prevent the formation of plaques, or prevent or delay the rupture of the plaques. Thus, the skilled person would not interpret the results presented by Rossoni *et al.* in such a way that they indicated that treatment with BAY-X-1005 could reduce CRP levels in a human subject at risk for MI. Succinctly put, a study of a drug's effect *while* (or after) surgically mimicking MI in rabbits provides no guidance whatsoever about the possible effects of the drug for reducing an inflammatory marker (CRP) in a human **at risk for** MI.

The rabbit coronary ligation model is not a model of humans *at risk* for MI, as recited in the claims, so it is entirely unpredictable to extrapolate from Rossoni *et al.* the effect of a drug in a human who is merely at risk for MI. The study in Rossoni *et al.* was carried out on an otherwise healthy rabbit heart in which the coronary artery was ligated to induce an acute MI. The rabbits are herbivores that are not affected by the same genetic and environmental risk factors for cardiovascular disease as human subjects at risk for MI who would receive BAY-X-1005 to reduce CRP levels using the claimed methods (Russell & Procter, *Cardiovas. Res.* 15: 318-330, 2006; provided as Exhibit B in previous response). Rossoni *et al.* is one experiment carried out in a healthy rabbit heart that was surgically blocked, and therefore would not render the claimed methods of administering BAY-X-1005 to reduce CRP in humans at risk for MI obvious (alone or in combination) with any of the references cited by the Examiner.

6. Muller-Peddinghaus *et al.*

The citation of the Muller-Peddinghaus *et al.* reference that is being applied as a reference is incomplete, preventing detailed comment. The reference is cited as teaching that BAY-X-1005 is an orally active inhibitor of leukotrienes. The Examiner does not assert

that the reference teaches anything about the effect of this compound on CRP in human subjects at risk for MI, or any other population.

7. Gompertz et al.

The Examiner continues to cite to Gompertz *et al.* as a teaching to monitor leukotrienes in the serum of patients. The Gompertz *et al.* reference also does nothing to negate patentability (alone or in combination with other references). Gompertz *et al.* does demonstrate that BAY-X-1005 is effective in humans at reducing a measurable leukotriene, LTB4. However, Gompertz *et al.* was a study that looked at patients with *chronic obstructive pulmonary disease (COPD)*, a term referring to two *lung diseases*, chronic bronchitis and emphysema, that are characterized by obstruction to airflow that interferes with normal breathing. The present invention, in contrast, is about reducing CRP levels in a human at risk for MI. It is also worth noting that, while much of the Patent Office's discussion of Gompertz *et al.* focuses on monitoring blood, the Gompertz *et al.* study actually took measurements from *sputum* (which the Examiner acknowledges but continues to discuss blood and plasma). The mention of measurements from blood at page 293 is in the context of discussing a *different study* by Fischer *et al.*, cited in Gompertz *et al.*

8. Cunningham *et al.*

Finally, the Examiner cited Cunningham *et al.* (*J. Vet. Pharm. Therap.* 20: 296-307, 1997) to demonstrate that FLAP inhibitors such a s BAY-X-1005, induce concentration-dependent inhibition of ionophore-induced LTB4 production in whole blood. This reference confirms that production of a leukotriene, LTB4, decreases in response to administration of a leukotriene synthesis inhibitor. This reference is silent in regards to the effect of FLAP inhibitors on CRP levels. Thus, this reference fails to motivate one of skill in the art to administer BAY-X-1005 to reduce CRP levels in combination with monitoring leukotriene levels.

9. The Invention is Not Obvious in View of the Combination of Hatzelmann, Mazzone, Pietila, Rossoni, Muller-Peddinghaus, Gompertz, and Cunningham.

The Examiner asserted that it would have been obvious to combine Rossoni *et al* , Muller-Peddinghaus *et al.*, Gompertz *et al.*, and Cunningham *et al.,* because they all

pertain to BAY-X-1005 to inhibit leukotriene levels. Even if this were sufficient for combining these four references, the Examiner has failed to explain why it would have been obvious to combine these references with the other cited references that do NOT pertain to BAY-X-1005.

The Examiner asserts that the combination of all of the above-described references motivates a skilled artisan to monitor leukotriene levels in a patient before and during administration of a leukotriene synthesis inhibitor. However, the claims are directed to administering a leukotriene synthesis inhibitor to reduce CRP. None of the cited references alone, or in any combination, provide any teaching or suggestion that administration of a leukotriene synthesis inhibitor would reduce CRP levels in a human subject at risk of MI. The only reference pertaining to CRP, Pietila, contemplates use of *thrombolyic treatment* to reduce inflammatory reaction, *post*-MI.

The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success." *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006). If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art. (See also MPEP § 2143(g) and the U.S.P.T.O. Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court's *KSR Intl. v Teleflex Inc.* Fed. Register Vol. 72, No. 195, October 10, 2007). As established above, none of these findings can properly be made here, because there is no motivation to combine; the combination does not suggest the current invention; and there is no indication in the prior art that the invention would be successful.

C. The Examiner Failed to Consider Applicants' Arguments

In the Office Action dated June 1, 2007, the Examiner rejected the claims under 35 U.S.C. § 103 in view of a combination of Isakson *et al.* (US Patent No. 6,136,839) in view of Rossoni *et al.* (*J. Exp. Ther.* 276: 335-341, 1996), Muller-Peddinghaus *et al.* (*Pharm. Exp. Therp.*), Gompertz *et al.* (*Chest* 122: 289-294,2002), and Byrum *et al.* (*J. Exp. Med.* 185: 1065-1075, 1997). In response, the Applicants provided detailed arguments as to

why these references are irrelevant to the claimed invention and do not alone or in combination render the claims obvious. Although the prior rejections appear to have been withdrawn, the Examiner presented a new rejection under 35 U.S.C. § 103 in the present Office Action using all of the previously cited references other than Isakson *et al.* In the present office action, the Examiner did not discuss or rebut any of the Applicants' arguments relating to the references cited in the previous Office Action.

According to MPEP § 2142, the Examiner must consider the persuasiveness of any evidence supporting the patentability of the claimed invention, including attorney arguments and journal articles presented to support those arguments. See *In re Oetiker,* 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). Although the prior rejection was apparently withdrawn, the Patent Office has failed to address Applicants arguments as they relate to any of the references cited in the first action and cited again in the current action. Clarification for the record is requested, in case it is necessary to seek further review of the application.

For the reasons set out in response to the previous Office Action, the Applicants maintain that Rossoni *et al.*, Muller-Peddinghaus *et al.* Gompertz *et al.*, and Byrum *et al.* are irrelevant to the claimed invention and do not alone or in combination render the claims obvious.

D. The Invention is Not Obvious in View of the Combination of Hatzelmann, Mazzone, Pietila, Rossoni, Muller-Peddinghaus, Gompertz, and Byrum

The Examiner rejected claims 225, and 227-228 under 35 U.S.C § 103 as being unpatentable in view of Hatzelmann *et al.*, Mazzone *et al.*, Pietila *et al.*, Rossoni *et al.*, Muller-Peddinghaus *et al.*, Gompertz *et al.*, Cummingham *et al.* and Byrum *et al.* (*J. Exp. Med.* 185: 1065-1075, 1997). Claims 225, 227-228 are directed to methods of reducing CRP in subject at risk for MI wherein the subject selected has a FLAP genotype or haplotype that correlates with an increased risk of MI.

The Examiner asserted that Hatzelmann *et al.* teaches that BAY-X-1005 is a five lipogenase activating protein, and one of oridinary skill understands that genes code for proteins (see page 8 of the Action). BAY-X-1005 is not a FLAP protein, it is a FLAP inhibitor.

The Examiner also asserted that Byrum *et al.* teaches the identification of the FLAP gene in mice and demonstated a reduced inflammatory response was observed in mice that were missing the FLAP geneotype. Therefore, the Examiner concluded that one of skill in the art would be motivated to administer BAY-X-1005 to a subset of patients that have a FLAP genotype.

The mice in Byrum *et al.* were "knockout" mice genetically manipulated to lack the FLAP gene. The Examiner has failed to cite any prior art that analogous human populations have been created in the laboratory (of course they have not), or were known to exist at the time that the invention was filed. Absent such connection, it is absurd to conclude that a person of ordinary skill would have concluded anything about human FLAP genotypes form Byrum's knockout mouse study.

As stated in the previous response, claim 225 involves determining a FLAP genotype or haplotype of a human subject, and selecting for treatment a human subject with a FLAP genotype or haplotype that correlates with an increased risk of myocardial infarction. Byrum *et al.* made a FLAP knockout mouse. The ability to knockout a gene in laboratory mice has nothing whatsoever to do with human genotyping. Byrum *et al.* does not disclose or suggest determining a human FLAP genotype or haplotype at all; does not disclose or suggest that any human variation in FLAP genes exists; and does not disclose, suggest, or enable identifying a human FLAP genotype that correlates with an increased risk of MI. The existence and identification of such at-risk haplotypes is an invention of deCODE's and is the subject of this application and co-pending applications. The Examiner has failed to cite any reference that discloses or suggests that a human population can be stratified with respect to risk for MI based on polymorphisms or haplotypes in the FLAP gene.

Finally, but equally importantly, it must be noted that the Patent Office offered no reason why one of ordinary skill would have combined Byrum *et al.* with any other reference cited by the Patent Office.

E. Conclusion with Respect to Obviousness

The Patent Office has failed to cite any reference or reference combination that suggests that an inhibitor of FLAP activity in general, or BAY-X-1005 in particular, would be useful for reducing CRP levels in a human subject at risk for MI. The references cited by or referred to by the Examiner do not suggest that administration of BAY-X-1005 would reduce CRP levels in a human subject at risk for MI. None of the references mention reduction in CRP levels and do not teach one of skill in the art anything related to CRP levels. There is no link between these references and there is no reason for one of skill in the art to combine these references to carry out the claimed invention. Therefore, the claims are not obvious in view of the cited references and Applicants request that the rejection under 35 U.S.C. § 103 be withdrawn.

V. DOUBLE PATENTING REJECTIONS

The Applicants request that all provisional double patenting rejections be deferred until such time as there is an indication that subject matter is otherwise allowable in one of the pending applications. The Applicants will cancel claims or file terminal disclaimers if necessary to obviate a double patenting rejection.

CONCLUSION

In view of the foregoing remarks, the Applicants respectfully request reconsideration and withdrawal of all rejections and allowance of the claims currently under examination, as well as linked claims that should be rejoined upon allowance of the generic claims.

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